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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.				
10/559,857	12/07/2005	Mark E. Fraley	21405YP	1561				
210 MERCK AND CO., INC P O BOX 2000 RAHWAY, NJ 07065-0907	7590 08/22/2007		<table border="1"><tr><td colspan="2">EXAMINER</td></tr><tr><td colspan="2">LOEWE, SUN JAE Y</td></tr></table>		EXAMINER		LOEWE, SUN JAE Y	
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			<table border="1"><tr><td>MAIL DATE</td><td>DELIVERY MODE</td></tr><tr><td>08/22/2007</td><td>PAPER</td></tr></table>	MAIL DATE	DELIVERY MODE	08/22/2007	PAPER	
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08/22/2007	PAPER							

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

<b>Office Action Summary</b>	Application No. 10/559,857	Applicant(s) FRALEY ET AL.	
	Examiner Sun Jae Y. Loewe	Art Unit 1626	

**-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --**  
**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

- 1) ☒ Responsive to communication(s) filed on 7/19/2007.
- 2a) ☒ This action is **FINAL**.                      2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

- 4) ☒ Claim(s) 1-7 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☒ Claim(s) 5 is/are allowed.
- 6) ☒ Claim(s) 1-4, 6-7 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

#### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \*    c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

#### Attachment(s)

- |  |   |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)                     | 4) <input type="checkbox"/> Interview Summary (PTO-413)           |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____                                      |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)          | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____  | 6) <input type="checkbox"/> Other: _____                          |

### DETAILED ACTION

1. Claims 1-7 are pending in the instant application. Claim 5 is allowed. Claims 1-4, 6 and 7 are rejected.

#### *Amendments & Arguments*

2. Applicant's arguments submitted on July 19, 2007 were fully considered. The objection to claim 5 is withdrawn. Applicant's arguments in response to the objection of claims 1-4, 6 and 7 and the rejection of claims 1-4, 6 and 7 are not found persuasive. Both grounds of objection and rejection are maintained (see below sections 3 and 4).

#### *Elected and Examined Subject Matter*

3. An election of species was made on June 4, 2007 within the elected Group I, drawn to products. Applicant elected compound of example 8-2 found on p. 86 of the instant specification. Aside from the species elected, and the compounds indicated to be allowable in section 6 of the previous office action, other non-elected species were not found to be allowable. That is, a subgenus that includes the allowable compounds and selected non-elected species was searched and examined. The full scope of this subgenus was not in compliance with the requirements of 35 USC § 112 – Written Description. Pursuant to MPEP 1893.03(d), subject matter outside of this subgenus but within the scope of Group I was not rejoined. It is asserted that the subject matter not rejoined is patentably distinct and non-elected. Applicant's argument (below) is not found persuasive.

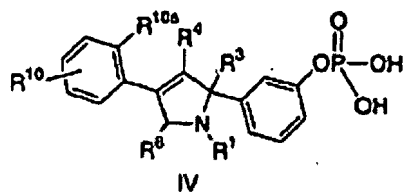
Applicant's response, dated May 31, 2007, the Applicants elected Group I, which contains Claims 1-4, 6 and 7. Accordingly, Applicants respectfully request that the objection of Claims 1-4, 6 and 7 be withdrawn.

The objection to claims 1-4, 6 and 7 for containing non-elected subject matter is maintained.

The scope of the elected and examined subject matter is shown in section 4 below.

*Claim Rejections – 35 USC § 112*

4. For clarity, the scope of subject matter searched in examined in the previous office action is shown below (ie. scope of claims).



R<sub>1</sub>=(C=O)C<sub>1-10</sub> alkyl or (C=O)NR<sub>c</sub>R<sub>c</sub>'.

The grounds of traversal in the response dated July 19, 2007 are addressed below.

a. Applicant interprets the scope of claims set forth in the office action as:

R<sup>3</sup>/R<sup>4</sup>/R<sup>8</sup>: Optionally substituted with any substituent including, for example R<sup>c</sup> and R<sup>c'</sup> and additional phosphate groups

For clarity, the scope of the claims set forth in the office action is transcribed below:

Further, variables like R<sub>3</sub>, R<sub>4</sub> and R<sub>8</sub> can be optionally substituted with any substituent including for example, those noted for R<sub>c</sub> and R<sub>c'</sub> as well as additional phosphate groups.

The statement “including for example, those noted for R<sub>c</sub> and R<sub>c'</sub>” was not intended to assert that R<sup>3</sup>, R<sup>4</sup> and R<sup>8</sup> are directly substituted with R<sub>c</sub> and R<sub>c'</sub>. Rather, it was intended to assert that R<sup>3</sup>, R<sup>4</sup> and R<sup>8</sup> may be substituted with groups that are also listed as options for the substituents R<sub>c</sub> and R<sub>c'</sub>: for example, aryl and heterocyclyl which are common to both R<sub>c</sub>/R<sub>c'</sub> and the possible substituents to R<sup>3</sup>, R<sup>4</sup> and R<sup>8</sup>.

In view this clarification, Applicant's traversal (below) does not apply.

However, Applicants respectfully maintain that  $R^3$ ,  $R^4$ ,  $R^8$  can only be substituted with a substituent selected from  $R^{10}$ , which does not include the variables  $R^C$  and  $R^C$ .

- b. Applicants state that the following provide for a correlation between structure and function:

respectfully assert that all the compounds claimed in the instant application share common structural attributes, including the same 2,5-dihydro-1H-pyrrole core structure. In addition, all compounds are prodrugs of KSP inhibitors that contain a common  $-OPO(OH)_2$  group. Therefore, the genus claimed in the instant application exhibits a correlation between structure and function, which is disclosed in the instant application.

Neither of the two structural attributes quoted by Applicant – the dihydropyrrole core and the presence of a  $-OPO(OH)_2$  group – gives guidance as to what specific structural modifications within the core structure shown above are tolerated for activity. It is not clear whether Applicant intends to state that all compounds within the genus claimed are active inhibitors of mitotic kinesin because the only requirement for activity within this genus is the presence of a dihydropyrrole core and a  $-OPO(OH)_2$  group. If the latter was the intended meaning, Applicant is invited to clarify this on the record. For the current office action, Applicant's statement will not be so interpreted. Thus, it is maintained that the instant specification does not disclose a correlation between structure and function.

- c. Applicant states:

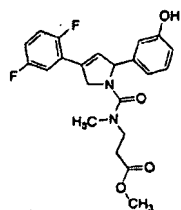
at least seven embodiments of  $R^{10}$

substitutions are illustrated in the examples, schemes and/or the preferred selection sections of the specification. Representative examples are illustrated below (non-exhaustive list):

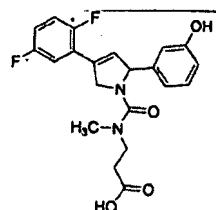
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For clarity, the compounds referenced by Applicant are noted below:

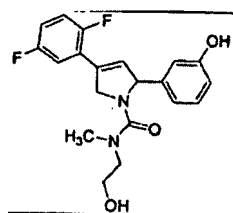
1.  $(C=O)_aObC1-C^{10}$  alkyl: Exemplified by Compound 4-5 (pg. 78)



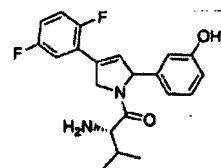
2.  $CO_2H$ : Exemplified by Compound 4-4 (pg. 77)



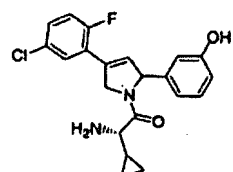
3. halo: Exemplified by Compound 4-3 (pg. 77)



4. OH: Exemplified by Compound 3-6 (pg. 73) & 5.  $O_2(C=O)_bNR^{12}R^{13}$ : Exemplified by Compound 3-6 (pg. 73)

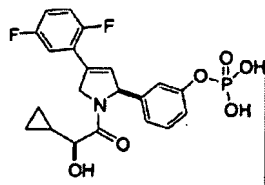


6.  $(C=O)_aObC3-C^8$  cycloalkyl: Exemplified by Compound 3-10 (pg. 74)



7.  $-OPO(OH)_2$ : Exemplified by Compound 8-3 (pg. 87)

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It is noted that compound of example 7 is the only compound that is encompassed by the instant claims, which requires the following

„ Provided that at least one substituent  $-OPO(OH)_2$  is present „ – claim 1, last entry on page 7.

For this compound,  $R_3=R_4=R_8=\text{hydrogen}$ ;  $R_c/R_c'$ =not applicable to this structure.

See further discussion on section 4e.

d. Applicant asserts:

at least four different  $R^C$  and  $R^C$  substituents were either included as examples or disclosed as a preferred embodiment in the specification. Representative examples are illustrated below (non-exhaustive list):

1. H:  $R^1$  is an aminocarbonyl (pg. 26, line 3) -  $R^C/R^C = H$
2.  $C_1-C_6$  alkyl:  $R^1$  is an N,N-dimethylaminocarbonyl (pg. 26, line 3) -  $R^C/R^C = CH_3$
3. Heterocyclyl: Exemplified by Compound 8-4 (pg. 87) -  $R^C/R^C =$  cyclopropyl
4.  $R^C$  and  $R^C$  are joined to form a monocyclic or bicyclic heterocycle: Exemplified by Compound 4-6 (pg. 78) -  $R^C/R^C =$  Morpholine

Note definition of heterocyclyl, instant specification p. 22:

The term "heterocycle" or "heterocyclyl" as used herein is intended to mean a 3- to 10-membered aromatic or nonaromatic heterocycle containing from 1 to 4 heteroatoms selected from the

Cyclopropyl does not contain a heteroatom, thus it is not representative of "heterocyclyl".

Morpholine does fall within the genus of:

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R<sup>c</sup> and R<sup>c'</sup> can be taken together with the nitrogen to which they are attached to form a monocyclic or bicyclic heterocycle with 3-7 members in each ring and optionally containing, in addition to the nitrogen, one or two additional heteroatoms selected from N, O and S, said monocyclic or bicyclic heterocycle optionally substituted with one, two or three substituents selected from R<sup>11</sup>;

however, it is only one example and as such it is not sufficient to support such a large and structurally diverse claimed genus.

See further discussion on section 4e.

- e. In view of Applicant's arguments addressed on sections c and d, further in view of the fact that the instantly claimed genus are prodrugs of KSP inhibitors, the scope of the disclosure in support of the claims is modified to include substituents exemplified for the KSP inhibitors:

R<sup>3</sup>/R<sup>4</sup>/R<sup>8</sup> = H or unsubstituted alkyl

R<sup>10</sup> = the following, not further substituted:

- 1) (C=O)<sub>a</sub>O<sub>b</sub>C<sub>1</sub>-C<sub>10</sub> alkyl,
- 6) CO<sub>2</sub>H,
- 7) halo,
- 9) OH,
- 11) O<sub>a</sub>(C=O)<sub>b</sub>NR<sup>12</sup>R<sup>13</sup>, wherein a=b=0; R<sup>12</sup>=R<sup>13</sup>=H or alkyl
- 17) (C=O)<sub>a</sub>O<sub>b</sub>C<sub>3</sub>-C<sub>8</sub> cycloalkyl, wherein a=b=0
- 18) -OPO(OH)<sub>2</sub>;

R<sup>12</sup> and R<sup>13</sup> = the following, not further substituted:

- 1) H,
- 2) (C=O)O<sub>b</sub>C<sub>1</sub>-C<sub>10</sub> alkyl, wherein b=0

R<sup>c</sup> and R<sup>c'</sup> = the following, not further substituted

H, (C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>3</sub>-C<sub>6</sub>)cycloalkyl

R<sup>c</sup> and R<sup>c'</sup> together with the nitrogen to which they are attached form morpholine



It is maintained that the variables to the core structure searched and examined (see above) are claimed broader than what is supported by the specification (eg. variables R3, R4, R8, R10, R11, R12, R13, Rc, Rc'). The 35 USC 112 Written Description rejection is maintained.

### ***Conclusion***

**5. THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.


Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sun Jae Y. Loewe whose telephone number is (571) 272-9074. The examiner can normally be reached on M-F 7:30-5:00 Est.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph McKane can be reached on (571)272-0699. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Sun Jae Y. Loewe, Ph.D.  
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REBECCA ANDERSON  
PRIMARY EXAMINER